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# Accepted Manuscript

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# **Transcutaneous electrical acupoint stimulation as an adjunct therapy for obsessive-compulsive disorder: a randomized controlled study**

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## Abstract

*Background:* Transcutaneous electrical acupoint stimulation (TEAS) is thought to have potential to treat obsessive-compulsive disorder (OCD).

*Objective:* The purpose of this study was to determine whether adding TEAS to cognitive behavioral therapy (CBT) and clomipramine would improve the efficacy of these conventional treatments in OCD.

*Methods:* In this randomized controlled trial, 360 OCD patients were assigned to receive TEAS combined with CBT plus clomipramine (Group A,  $n = 120$ ), TEAS combined with CBT plus placebo (Group B,  $n = 120$ ), and simulated (placebo) TEAS combined with CBT plus clomipramine (Group C,  $n = 120$ ) for 12 weeks. The primary outcome was measured using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS).

*Results:* OCD symptoms in all patients reduced over time, however Groups A and B had a significantly greater reduction in Y-BOCS total score and the subscale for obsession and compulsion between week 2 and week 12 compared to Group C. Groups A and B had similar scores on these measures. Both groups had significantly higher rates of clinical response than Group C (88.3% and 81.7% vs. 67.5%, respectively,  $p < 0.001$ ); and higher rates of remission (30.0% and 22.5% vs. 9.2%, respectively,  $p < 0.001$ ).

Group B experienced fewer adverse events than the other two groups.

*Conclusions:* TEAS enhances the efficacy of conventional OCD interventions and avoids the adverse effects associated with conventional pharmacological treatment. It can be considered as an effective adjunct intervention for OCD.

*Keywords:* Obsessive compulsive disorder (OCD); transcutaneous electrical acupoint stimulation (TEAS); transcutaneous electrical nerve stimulation (TENS); serotonin reuptake inhibitors (SRIs); cognitive behavioral therapy (CBT); clomipramine.

## 1. Introduction

Obsessive-compulsive disorder (OCD) is a disabling mental illness that affects approximately 1-2% of the general population (Lihua et al., 2013; Ruscio et al., 2010). It is characterized by recurrent, intrusive and senseless thoughts (obsessions) and/or excessive repetitive behaviors (compulsions) aimed at reducing the associated anxiety (APA, 2000). Despite the fact that serotonin reuptake inhibitors (SRIs), such as clomipramine, and cognitive behavioral therapy (CBT) are recommended as first-line treatments for OCD (Pizarro et al., 2014; Romanelli et al., 2014), there still remains a large portion of the patients who do not make a full response (Schruiers et al., 2005). A search for alternative strategies is thus important.

Although it is an ancient therapeutic technique, acupuncture has been increasingly included in the management of neurological and psychiatric disorders, such as pain, insomnia, anxiety and depression (Pilkington, 2013; van der Watt et al., 2008). Acupuncture methodology has also evolved along with the advances in modern science and technology (Han, 2011; Han et al., 1994; Han and Ho, 2011). Transcutaneous electrical acupoint stimulation (TEAS) has been developed to replace needle penetration (Han et al., 1994). TEAS is a form of transcutaneous electrical nerve stimulation (TENS), TEAS may be more effective than other forms of TENS in modulating brain activity, as acupoints contain relatively denser neural and neuroactive components than non-acupoint areas (Zhang et al., 2012). Unlike invasive acupuncture in which needles are inserted into acupoints on the body, TEAS is a non-invasive electrical stimulation that generally could not cause pain and needle phobia (Wang et al., 1992; Han, 2011). While TEAS is practiced in a noninvasive, safer and time-saving manner, its antinociceptive potency is reported to be equivalent to that of needling acupuncture with both approaches sharing similar mechanisms (Wang et al., 1992; Han, 2011). TEAS has

now been reported to have a beneficial effect in autism (Zhang et al., 2012), smoking cessation (Lambert et al., 2011), and drug dependence (Meade et al., 2010; Penetar et al., 2012). We and others have the preliminary evidence for the effectiveness of TEAS together with CBT and/or SRIs in phobia and OCD (Feng et al., 2005, 2006; Yamashita et al., 1991).

In this study we tested the hypothesis that adding TEAS to CBT and SRIs would improve the efficacy of these conventional treatment in OCD. To achieve this, we compared the outcomes of patients randomized to three treatment groups: Group A, TEAS + CBT + clomipramine; Group B, TEAS + CBT + placebo; and Group C, simulated TEAS + CBT + placebo, using a double-blind, controlled design. Clomipramine is a commonly prescribed SRI for OCD with well-established efficacy for the treatment of OCD (Pizarro et al., 2014).

## **2. Materials and methods**

### *2.1. Settings and participants*

This multisite, partially double-blind, randomized controlled trial was conducted between September 2009 and December 2012 in 3 hospitals: Zhejiang Provincial Tongde Hospital, Yiwu Hospital of Traditional Chinese Medicine (TCM), and Wuxi Mental Health Center. The study protocol was approved by Medical Ethical Committee of all hospitals involved and registered in [www.chictr.org](http://www.chictr.org) (ChiCTR-TRC-09000484), a member of the WHO International Clinical Trial Registry Platform. The study was carried out in accordance with the approved protocol. All participants and/or their guardians gave voluntary, written, informed consent before entering the trial.

Both outpatients and inpatients were invited to participate in the study. Eligible subjects were (1) either gender aged 16-65 years with (2) a principal diagnosis of OCD of

duration  $\geq 1$  year, according to the Classification of Mental and Behavior Disorders (10th version) (ICD-10) (WHO, 1995). (3) The severity of participants' symptoms was at least moderate, as evidenced by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score of  $\geq 16$  (Farris et al., 2013; Goodman et al., 1989a,b); and (5) All had capacity to give written informed consent.

Patients who had any of the following conditions were excluded: (1) OCD was only a comorbid symptom, but the "primary" psychiatric disorders were not OCD. The "primary" disorders included schizophrenia, mood disorders, tic disorders, movement disorders, eating disorders, and mental retardation; (2) severe cardiovascular, hepatic, renal condition, or narrow-angle glaucoma; (3) a history of brain injury or surgery; (4) a history of suicide attempts or aggressive behavior; (5) pregnancy or lactation; (6) laboratory tests of hepatic and renal function and/or electrocardiogram (ECG) significantly beyond the normal reference ranges; (7) investigational drug treatment within the previous 6 months; (8) a history of alcohol or drug abuse within the previous 12 months; or (9) heart pacemaker or other metal devices implanted in the body.

## 2.2. Randomization and blinding

Patients were randomly allocated to 1 of 3 groups: Group A, TEAS combined with CBT plus clomipramine; Group B, TEAS combined with CBT plus placebo tablets (Group B); and Group C, simulated TEAS combined with CBT plus clomipramine (Group C) in a ratio of 1:1:1. For randomization, simple, complete, non-sequential random codes were produced in advance using a computer-generated block scheme in which treatment groups were kept in balance for every 6 entrants at each site. Drug dispensers, clinical raters, data collectors and analysts were blinded to the treatment; behavioral therapists were blinded to patients' medications and TEAS (see below).

The group allocation was done in a double-blind manner. For medications, random codes were printed on boxes containing clomipramine and placebo tablets. All study personnel, including drug dispenses, clinical assessors, data collector and analysts, were blind to patients' medication status. However, assignment to TEAS or stimulated stimulation was known to the therapists who carried out these procedures, but no other personnel. Patients were not aware of their assignment to either TEAS or simulated stimulation. They were told that they would receive electrical stimulation on both hands, but they were not told that the stimulation might be simulated or real. Behavioral therapists, clinical assessors and psychiatrists communicated with patients separately and were instructed not to acquire information about their other treatment conditions.

### 2.3. Intervention

*Clomipramine treatment:* Both clomipramine and placebo tablets were manufactured by Hunan Dongting Pharmaceutical Co., Ltd. (Changsha, Hunan, China). Both were prepared to be identical in appearance, odor, flavor and color. Clomipramine was initiated at a dosage of 25 mg/day and titrated up to a maximum of 150 mg/day within 16 days, depending on clinical and side effects. This dosing regimen of clomipramine has been well established to achieve a balance between the therapeutic benefits and adverse effect risk for the treatment of OCD in Chinese population (Feng et al., 2006). Group A and C received clomipramine treatment; Group B was given matching placebo tablets.

Those who were currently treated with clomipramine continued their clomipramine treatment, but the dose would not exceed 150 mg/day. Those who were currently treated with other anti-OCD drugs were instructed to switch to the clomipramine treatment regimen by gradually withdrawing the current drugs within one week. This washout period was sufficient to eliminate carryover effects of most antipsychotics and selective



serotonin reuptake inhibitors (SSRIs) (Hiemke & Härtter, 2000; Mauri et al., 2014). Concomitant use of other psychoactive agents was not allowed. Medication compliance was determined with tablet count at each visit. Patients required concomitant medications and those with <80% compliance were advised to withdraw from the study.

*CBT*: Patients from all 3 groups received CBT consisting of exposure and response prevention (EX/RP) according to standard care in OCD (Franklin et al., 2002); but the number of treatment sessions was adapted to 12 sessions (once weekly) with each session lasting 45 min, based on clinical characteristics in Chinese patients with OCD and Chinese cultural context (Guo and Lanley, 2015; Ma et al., 2013; Zhang et al., 2013]. The adapting CBT has been widely used in China (Guo and Lanley, 2015; Ma et al., 2013). Briefly, session 1-2 included introduction to the treatment procedure, cognitive training and identifying OCD target symptoms. In Session 3-12, patients were instructed to face their obsessional fears induced with imagined and real scenarios. Patients were always encouraged to actively control and stop obsessive thoughts and ritual behavior during the exposure. The intensity of the exposure was gradually increased when anxiety had reduced to a negligible level in the preceding trial. A family member was asked to be involved in the treatment whenever possible. Homework with at least 30 min of self-directed exposures daily was assigned between sessions to enhance patients' motivation and prevent relapse.

In order to ensure consistency of CBT delivery across study sites, a pretrial training workshop was held for psychiatrists and behavioral therapists who performed CBT. The detailed explanation of EX/RP procedure and rehearsal with real patients was conducted under the supervision of a senior behavioral therapist (B.F.).

*TEAS and simulated stimulation:* Patients in Group A and B received TEAS and Group C received simulated stimulation. TEAS and CBT treatment were conducted simultaneously by CBT therapists (Fig. 1). TEAS was delivered on the bilateral Nei-Guan (PC6) which is located on the anterior forearm, between the tendons of palmaris longus and flexor carpi radialis, at the junction of the distal sixth and proximal five sixths of the line connecting the middle points of the wrist and elbow crease (Liu & Liu, 2009). According to traditional Chinese medicine, this acupoint is particularly beneficial for sleep, sadness, nervousness, palpitation, chest congestion, nausea and vomiting (Liu & Liu, 2009). Neuroimaging studies have shown that acupuncture stimulation on this acupoint can modulate a wide range of cortical and limbic brain region activity (Chang et al., 2009; Quirico et al., 2014; Yoo et al., 2004; Zhang et al., 2012). Constant-current electrical impulses produced from a battery-driven TEAS apparatus (NDK, Osaka, Japan) were delivered on bilateral acupoints via two adhesive electrode pads placed on the acupoint skin (Fig. 1). The stimulation frequency was set at 50 Hz with pulse width of 50  $\mu$ s. The choice of this frequency was based on our preliminary experiments comparing acceptability of different frequencies (2-100 Hz). This frequency range has also been shown to robustly induce the release of endogenous opiate neuropeptides in the central nervous system (Han, 2003). The pulse amplitude (0-100mA) was titrated to a level at which the perception of 'strong but comfortable' was achieved.

Transient placebo-TENS was applied for simulated stimulation (Rakel et al., 2010). Adhesive electrode pads were placed at sites 1 cm radial to Nei-Guan (PC6) and the stimulation intensity was adjusted to the minimal sensory threshold for 30 seconds and then ramped off over the next 15 seconds so that it was active for a total of 45 seconds. This transient placebo-TENS has been well validated and found to better maintain blinding compared to standard placebo-TENS methods, in which no current was actually delivered to the electrodes (Rakel et al., 2010).

#### *2.4. Treatment outcome measures*

Treatment outcomes were evaluated at baseline, week 2, 4, 8 and 12. The primary outcomes were the total score on the Y-BOCS and subscales for obsession and compulsion (Goodman et al., 1989a,b). The secondary outcomes were clinical response and remission. As previously described (Farris et al., 2013), a clinical response was defined as a  $\geq 35\%$  reduction at endpoint from baseline on Y-BOCS total score. Remission was defined as an endpoint Y-BOCS score of  $\leq 12$ . Laboratory tests, including hepatic and renal functions, ECG and EEG, were conducted at baseline and the completion of treatment. Safety was assessed using the Treatment Emergent Symptom Scale (TESS) (Guy 1976), in which adverse events that first appeared during the study or worsened relative to the pre-study status were recorded at each visit, including date and time of onset, duration, severity, relationship to intervention, and action taken accordingly.

Clinical assessment was performed by three raters (F.Z.X., L.X.Z., and Y.Y.L.) who were blinded to the treatment. To ensure consistency of assessment across sites, a training workshop was carried out on videotaped patients with OCD before the recruitment started. Independent assessors from all study sites had achieved an inter-rater reliability coefficient ( $\kappa$  value) of  $>0.80$  on Y-BOCS after the completion of training workshop. In most cases, all assessments of a subject from baseline to endpoint were conducted by the same assessor in order to minimize potential variations caused by different assessors.

#### *2.5. Statistical analysis*

The sample size estimation was based on clinical response rate. Based on our previous studies (Feng et al., 2005, 2006), we expected that the addition of TEAS could produce an approximately 20% higher clinical response rate than simulate stimulation. A sample size of 360 was calculated to provide an approximately 90% power at a statistical level of 0.01.

Data analysis was conducted by H.K.W. who was blinded to the treatment. Efficacy analyses were performed on the intention-to-treat population, defined as participants who completed baseline and at least one evaluation after treatment. A linear mixed-effect model was applied to compare the primary treatment outcomes (Y-BOCS and its subscales for obsession and compulsion) over time among the 3 groups. The model was established using time and group for categorical fixed factors and random intercepts with scaled identity covariance matrix. Subject's age, gender and baseline Y-BOCS served as covariates. One-way analysis of variance (ANOVA) was further used to detect between-group differences among the 3 groups in continuous variables. Categorical variables, including categorical baseline variables, response and remission rates, and incidence of adverse events were analyzed using Chi-square ( $\chi^2$ ) test. Statistical significance was defined as a two-tailed  $P < 0.05$ . The analysis was conducted with SPSS version 19.0 software (SPSS Inc., Chicago, IL, USA).

### 3. Results

#### 3.1. Participant characteristics

Of 1435 patients screened, 360 eligible patients were recruited from Tongde Hospital (n = 200), Yiwu Hospital of TCM (n = 80) and Wuxi Mental Health Center (n = 80). The patients were randomly assigned to one of the three groups (n = 120 each); 335 (93.1%) completed the full 12 weeks of treatment and assessment (Fig. 2); 6.9% (25/360) discontinued treatment. No statistically significant difference was observed among the three groups in discontinuation rate (Fig. 2).

The sample was representative of young adults with OCD, as indicated by the mean (SD) age of 33.7 ( $\pm 12.4$ ) years, the mean duration of the illness of 5.0 ( $\pm 5.6$ ) years and the

Y-BOCS severity of 27.0 ( $\pm 5.3$ ) indicative of moderate to severe illness. A majority of patients (68.1%, 245/360) were under psychotropic medication when entering the study; only 2 were being treated with clomipramine. A small percentage of patients (6.1%, 22/360) had a diagnosis of comorbid psychiatric disorders. There were no statistically significant differences in baseline variables among the three groups (Table 1) or among the three study sites (data not shown). No participants received CBT when they entered the trial.

Overall medication compliance was approximately 95% across the three groups. No patients were excluded due to the poor compliance (less than 80%). The mean doses of clomipramine taken were 143.9 (17.6) mg/day for Group A and 141.7 (21.3) mg/day for group C ( $t_{1,238} = 0.884$ ,  $P = 0.378$ ). Those who completed the full 12 weeks of treatment also completed the full CBT sessions as per protocol.

### 3.2. Treatment outcomes

The primary outcomes are illustrated in Table 2 and Fig. 3. Linear mixed-effect model revealed significant differences in the slope among the 3 groups on total Y-BOCS ( $F = 9.128$ ,  $p = 0.0001$ ), obsession ( $F = 5.755$ ,  $p = 0.0032$ ) and compulsion ( $F = 13.389$ ,  $p < 0.0001$ ). The three variables strikingly reduced over the course of treatment for each group ( $p < 0.001$ ). Between-group comparisons revealed a significantly greater reduction in Y-BOCS total score and score on obsession and compulsion subscales on Group A and Group B at all post-treatment measurement points compared to Group C ( $p < 0.001$ ); but the 3 variables were not statistically different between Groups A and B at any post-treatment measurement points ( $p \geq 0.053$ ).

Both Groups A and B had markedly higher rates of clinical response than Group C [89.2% (107/120) and 82.5% (99/120) vs. 67.5% (81/120),  $F = 18.283$ ,  $df = 2$ ,  $p < 0.001$ ]

and remission [29.2% (35/120) and 22.5% (27/120) vs. 9.2% (11/120),  $F = 15.396$ ,  $df = 2$ ,  $p < 0.001$ ) (Fig. 4). No statistically significant differences were noted between Groups A and B in clinical response ( $F = 1.679$ ,  $df = 1$ ,  $p = 0.195$ ) and remission rate ( $F = 1.066$ ,  $df = 1$ ,  $p = 0.302$ ).

### 3.3. Adverse events

No severe adverse events were reported. The incidence of adverse events is summarized in Table 3. Both Group A and C exhibited significantly higher incidence of somnolence, tremor, dry mouth, blurred vision, constipation and laboratory test abnormality, the incidence was not significantly different in Group A and C.

## 4. Discussion

Serotonin reuptake inhibitors (SRIs), CBT, and their combination are first-line treatments for OCD (Pizarro et al., 2014; Romanelli et al., 2014). The first aim of the present study was to determine whether adding TEAS to the standard treatment could enhance the therapeutic response. We found that, while there was a significant improvement in OCD symptoms over the course of treatment in all three groups, the combination of three treatment regimens yielded much better outcomes compared with the standard treatment. That is, Group A had a significantly greater reduction in Y-BOCS total scores and subscales for obsession and compulsion at all post-treatment measurement points than Group C. The clinical response and remission rates of Group A were also markedly higher than Group C; whereas the mean dosages of clomipramine taken and the incidence of adverse events were similar in the two groups. These results indicate that additional TEAS has superior efficacy compared to standard therapy without causing additional side effects.

SRI therapy often causes undesirable side effects (Murphy et al., 2008). The present study further examined whether CBT plus TEAS but without clomipramine could achieve better safety profile and comparable efficacy relative to clomipramine-contained treatment regimens. As expected, Group B experienced much fewer adverse events compared to the other two groups. The adverse events reported included somnolence, tremor, dry mouth, blurred vision, constipation and laboratory test abnormalities, all of which often occur in clomipramine and other SRI therapy (Murphy et al., 2008). On the other hand, Group B had a significantly greater reduction in symptom severity than Group C; the response and remission rates of Group B were also statistically greater than Group C, but not different from Group A. These results suggest that, while TEAS combined with CBT reduces adverse side effects associated with clomipramine, the therapeutic response achieved is comparable and even superior to that of the standard treatment. It appears that TEAS mainly augments the therapeutic efficacy of CBT.

Modulation of brain serotonergic (5-HT) and related neuropeptidergic systems and normalization of sensorimotor gating may contribute to the effects of TEAS in improving OCD observed in the present study. Brain 5-HT systems are thought to play the principal role in the pathogenesis of OCD and related conditions; and SRI treatment effectively alleviates OCD symptoms (Camilla d'Angelo et al., 2014). Brain neuropeptides are also heavily involved in the development of obsessive thoughts and compulsive behavior, in particular vasopressin, oxytocin, adrenocorticotrophic hormone (ACTH), corticotropin releasing factor (CRF), somatostatin and opioids; and SRIs are believed to also act these neuropeptide systems (McDougle et al., 1999). TEAS is thought to accelerate the synthesis and release of 5-HT and norepinephrine (NE) in the brain (Han, 2011). TEAS treatment may prevent lowering 5-HT and catecholamines in depressed patients (Markelova et al., 1985; Song et al., 2007) and in animal models of depression (Dos Santos et al., 2008), and potentiate antidepressant effects in depressed

patients (Yu et al., 2006, 2007). TEAS broadly modulates hypothalamic and limbic neuropeptide functions, in particular vasopressin and oxytocin (Han, 2011; Zhang et al., 2012; Ulett et al., 1998). Thus, the improvement in OCD following combined treatment with clomipramine and TEAS may be due to additive effects on 5-HT and neuropeptide systems.

Sensorimotor gating is the process by which a neural system (mainly cortico-striato-thalamo-cortical circuits) screens or ‘filters’ extraneous external (sensory) and internal (cognitive, motor) impulses to prevent an overload of irrelevant information in the higher cortical centers of the brain (Ahmari et al., 2012). In OCD, impaired sensorimotor gating is postulated to cause cortical hyperexcitability and deteriorate inhibitory control, resulting in the inability to inhibit undesired thoughts and images (obsessions) and repetitive acts or reactions to uncontrollable obsessive thoughts (compulsions) (Ahmari et al., 2012; Kohl et al., 2013). CBT improves prepulse inhibition (PPI), an operational index of sensorimotor gating, in other psychiatric conditions (Ahmari et al., 2012; Kumari et al., 2012). Somatosensory evoked potentials (SEPs) is a potential biomarker for impaired sensorimotor gating of OCD patients (Rossi et al., 2005). Transcutaneous electrical nerve stimulation (TENS) on the median nerve induced SEPs, resulting in delayed gating effects on cortical response (Torquati et al., 2007). TENS also broadly modulated sensorimotor brain network activity, including the somatosensory cortex, basal ganglia, and thalamus (Choi et al., 2016; Dhond et al., 2008; Fang et al., 2009; Kara et al., 2010), and cortical neuronal excitability (Veldman et al., 2014). It appears that TENS, in particular TEAS, is capable of repairing ‘filtering’ dysfunction of the sensorimotor gating via enhancing 5-HT and neuropeptide functions in related brain regions. Therefore, again the combination of interventions, in this case TEAS plus CBT, may reinforce the improvement in sensorimotor gating in OCD.



Several limitations of the current study should be considered. First, we did not include a group treated with clomipramine alone as a positive control; although Group B treated with placebo tablets served a negative control for pharmacotherapy. However, several studies have compared CBT, SRIs and their combination, and have shown limited efficacy of SRIs as monotherapy for OCD (Simpson et al., 2013). Second, a much smaller percentage of our patients had a diagnosis of comorbid psychiatric conditions compared to OCD studies of adults in the United States (Simpson et al., 2013). However, this reflects epidemiological findings which may be due to the diagnostic instruments used for comorbid conditions, as well as ethnic and psychological traits (Xiaoli et al., 2014). One recent study has shown that only 15.2% children and adolescents had two or more psychiatric comorbid disorders in China (Xiaoli et al., 2014). Third, while the well-established dosing regimen of clomipramine was administered in the present study, the maximum dose was much lower than those previously reported, with a maximum of 250-300 mg/day (Pizarro et al., 2014). This may represent an ethnic difference in tolerability to this drug, largely due to variations in cytochrome P450 enzymes (Lambert & Norman, 2013). Fourth, the sampling frame was mainly restricted to young adults recruited from local Chinese communities that may have distinctive perceptions on acupuncture therapy. Whether TEAS treatment outcomes are related to patients' expectation and whether similar treatment outcomes could be achieved in OCD children and adolescents needs further investigation. Finally, a large portion of OCD patients may develop treatment-resistant cases who cannot achieve satisfactory improvement from CBT, SRIs, and even a combination of both (Tundo et al., 2007). However, the present did not analyze this subgroup. Whether the three component regimen could benefit treatment-resistant OCD deserves further evaluation.

In summary, additional TEAS enhanced the efficacy of CBT and SRI combination therapy in OCD. TEAS combined with CBT reduced adverse side effects associated

with pharmacotherapy for OCD; the therapeutic response achieved was at least comparable and even superior to that of CBT and SRI combination therapy. The three component regimen can be considered an effective treatment option for OCD.

### **Contributors**

BY and ZZJ were involved in conception and design of the study, data analysis and preparation of the manuscript. RMZ, GZY, LiYL, FZX, JC, LYL, YYL, YZ, and LXZ recruited subjects, conducted clinical assessment, and collected data. HKW performed data analysis. GMM provided critical comments on the paper.

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### **Conflict of interest**

The author(s) declare that they have no competing interests in the study.

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None.

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### Legends for figures

**Fig. 1.** Transcutaneous electrical acupoint stimulation (TEAS) on bilateral Nei-Guan (PC6) acupoints and cognitive-behavioral therapy (CBT) were conducted simultaneously for OCD patients. In this case, while TEAS was conducted on the patient's hands (A), he was encouraged to hold trash can (B).

**Fig. 2.** Flowchart of screening and recruitment of study subjects with OCD. Group A, transcutaneous electrical acupoint stimulation (TEAS) combined with cognitive-behavioral therapy (CBT) plus clomipramine; Group B, TEAS combined with CBT plus placebo tablets; and Group C, simulated TEAS combined with CBT plus clomipramine.

**Fig. 3.** The primary outcomes of OCD patients are illustrated with changes over the 12-week course of treatment in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score and subscale for obsession and compulsion. Overall statistical significance was determined using the linear mixed-effect model analysis. Group A, transcutaneous electrical acupoint stimulation (TEAS) combined with cognitive-behavioral therapy (CBT) plus clomipramine; Group B, TEAS combined with CBT plus placebo tablets; and Group C, simulated TEAS combined with CBT plus clomipramine. \* vs. Group C:  $p < 0.05$ .

**Fig. 4.** The rates of clinical response and remission in OCD patients. Group A, transcutaneous electrical acupoint stimulation (TEAS) combined with cognitive-behavioral therapy (CBT) plus clomipramine; Group B, TEAS combined with CBT plus placebo tablets; and Group C, simulated TEAS combined with CBT plus clomipramine. Data were analyzed using Chi-square ( $\chi^2$ ) test. \*  $p < 0.05$  vs. Group C.



**Table 1**  
Baseline characteristics of OCD patients <sup>a</sup>

Variables	Group A (n = 120)	Group B (n = 120)	Group C (n = 120)	<i>t</i> or $\chi^2$ value	<i>P</i> value
Male, n (%) <sup>b</sup>	52 (43.3)	67 (55.8)	52 (43.3)		0.720
Age (y) <sup>c</sup>	33.9 ± 11.7	31.9 ± 12.8	35.4 ± 12.6	2.510	0.083
Duration of the illness, n (%) <sup>a</sup>					
≥1 years	55 (45.8)	52 (43.4)	61 (50.8)	3.141	0.535
≥3 years	40 (33.4)	49 (40.8)	39 (32.5)		
≥10 years	25 (20.8)	19 (15.8)	20 (16.7)		
No. (%) of patients with comorbid psychiatric disorders <sup>b,d</sup>	7 (5.8)	11 (9.2)	4 (3.3)	3.583	0.167
No. (%) of patients with family members having severe mental problems <sup>b</sup>	6 (5.0)	11 (9.2)	4 (3.3)	3.944	0.139
No. (%) of patients under psychotropic medication when entry <sup>b,e</sup>	90 (75.0)	78 (65.0)	77 (64.2)	4.012	0.135
OCD symptom types, n (%) <sup>b</sup>					
Obsessional thoughts	72 (60.0)	77 (64.2)	72 (60.0)	0.586	0.746
Compulsive behaviors	48 (40.0)	43 (35.8)	48 (40.0)		
Baseline Y-BOCS total score <sup>c</sup>	27.1 ± 4.9	26.9 ± 4.6	27.0 ± 3.7	0.080	0.923
Baseline score on obsessive subscale <sup>c</sup>	14.1 ± 2.4	14.0 ± 2.4	13.8 ± 2.0	0.666	0.515
Baseline score on compulsive subscale <sup>c</sup>	13.0 ± 2.8	12.9 ± 2.4	13.2 ± 2.0	0.625	0.536

<sup>a</sup> Group A received transcutaneous electrical acupoint stimulation (TEAS) combined with cognitive-behavioral therapy (CBT) plus clomipramine; Group B received TEAS combined with CBT plus placebo tablets; and Group C received simulated TEAS combined with CBT plus clomipramine.

<sup>b</sup> Categorical data were analyzed using Chi-square ( $\chi^2$ ) test.

<sup>c</sup> Continuous data are expressed as mean ± SD and examined using one-way analysis of variance (ANOVA).

<sup>d</sup> Comorbid psychiatric conditions included tic disorders, generalized anxiety disorders, and major depression.

<sup>e</sup> Most patients were medicated with selective serotonin reuptake inhibitors (SSRIs) and antipsychotic agents. Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

**Table 2**Treatment outcomes measured using Y-BOCS in OCD patients <sup>a</sup>

Variables	Group A (n = 120)	Group B (n = 120)	Group C (n = 120)	Overall analysis <sup>b</sup>	
				$F_{2,1794}$	$p$
Total Y-BOCS score <sup>c</sup>				9.128	0.0001
Baseline	27.1 ± 4.9	26.9 ± 4.6	27.0 ± 3.7		
Week 2	17.6 ± 2.48*	19.0 ± 2.4*	23.3 ± 3.5		
Week 4	14.8 ± 2.2*	16.4 ± 2.7*	20.1 ± 3.2		
Week 8	13.7 ± 2.7*	15.4 ± 2.9*	18.2 ± 3.0		
Week 12	13.2 ± 2.9*	14.8 ± 3.4*	16.7 ± 3.5		
Obsession severity				5.755	0.0032
Baseline	14.1 ± 2.4	14.0 ± 2.4	13.8 ± 2.0		
Week 2	9.4 ± 1.4*	9.9 ± 1.3*	12.0 ± 2.1		
Week 4	8.0 ± 1.4*	8.6 ± 1.5*	10.3 ± 2.0		
Week 8	7.5 ± 1.6*	8.1 ± 1.6*	9.3 ± 2.0		
Week 12	7.2 ± 1.6*	7.8 ± 1.8*	8.6 ± 2.2		
Compulsive severity				13.389	<0.0001
Baseline	13.0 ± 2.8	12.9 ± 2.4	13.2 ± 2.0		
Week 2	8.2 ± 1.7*	9.1 ± 1.4*	11.4 ± 2.1		
Week 4	6.8 ± 1.5*	7.8 ± 1.5*	9.8 ± 2.1		
Week 8	6.3 ± 1.7*	7.3 ± 1.6*	8.8 ± 1.9		
Week 12	5.9 ± 1.9*	7.0 ± 1.9*	8.2 ± 2.1		

<sup>a</sup> Group A received transcutaneous electrical acupoint stimulation (TEAS) combined with cognitive-behavioral therapy (CBT) plus clomipramine; Group B received TEAS combined with CBT plus placebo tablets; and Group C received simulated TEAS combined with CBT plus clomipramine.

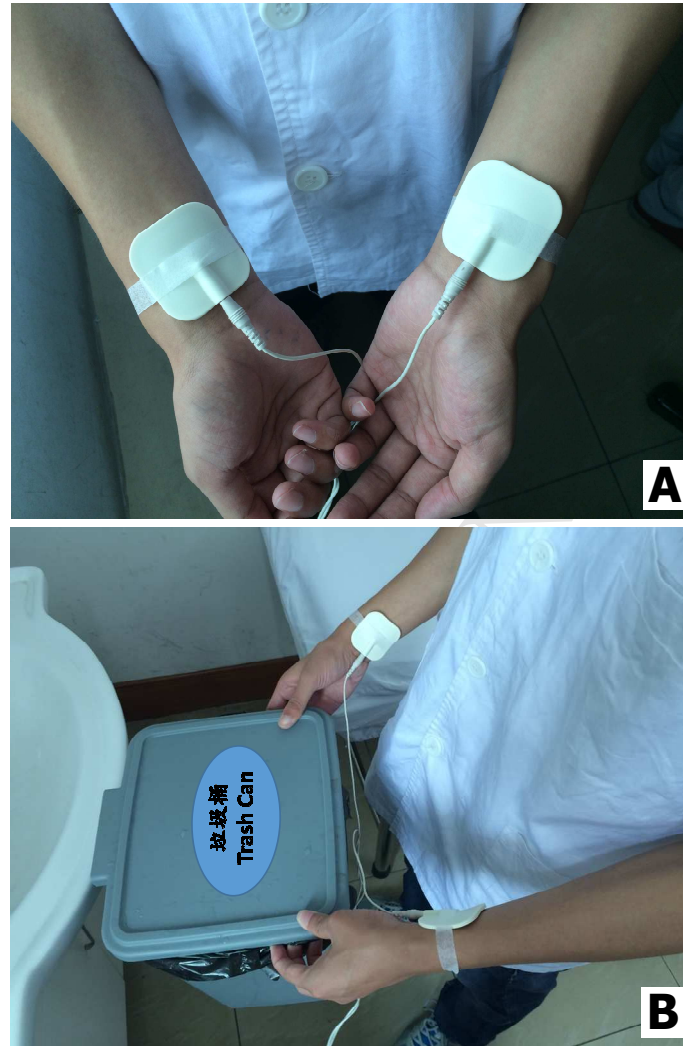
<sup>b</sup> Overall statistical significance was analyzed using a linear mixed-effect model analysis. Between-group differences were further evaluated using one-way analysis of variance (ANOVA). \* vs. Group C;  $p < 0.05$ .

<sup>c</sup> Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

**Table 3**The incidence of major treatment-emergent adverse events in OCD patients <sup>a</sup>

Adverse event	Group A (n = 120)	Group B (n = 120)	Group C (n = 120)	$\chi^2$ value	<i>p</i> value
Somnolence	14 (11.7)	2 (1.7)	13 (10.8)	9.976	0.007
Tremor	9 (7.5)	0	13 (10.8)	12.878	0.002
Dry mouth	47 (39.2)	13 (10.8)	41 (34.2)	27.194	<0.001
Blurred vision	23 (19.2)	8 (6.7)	15 (12.5)	8.424	0.015
Constipation	24 (20.0)	8 (6.7)	28 (23.3)	13.440	0.001
Dizziness	7 (5.8)	4 (3.3)	8 (6.7)	1.445	0.486
Skin problems	11 (9.2)	12 (10.0)	9 (7.5)	0.480	0.787
Laboratory test abnormality	9 (7.5)	0	12 (10.0)	11.833	0.003

<sup>a</sup> Group A received transcutaneous electrical acupoint stimulation (TEAS) combined with cognitive-behavioral therapy (CBT) plus clomipramine; Group B received TEAS combined with CBT plus placebo tablets; and Group C received simulated TEAS combined with CBT plus clomipramine.

**Fig. 1**

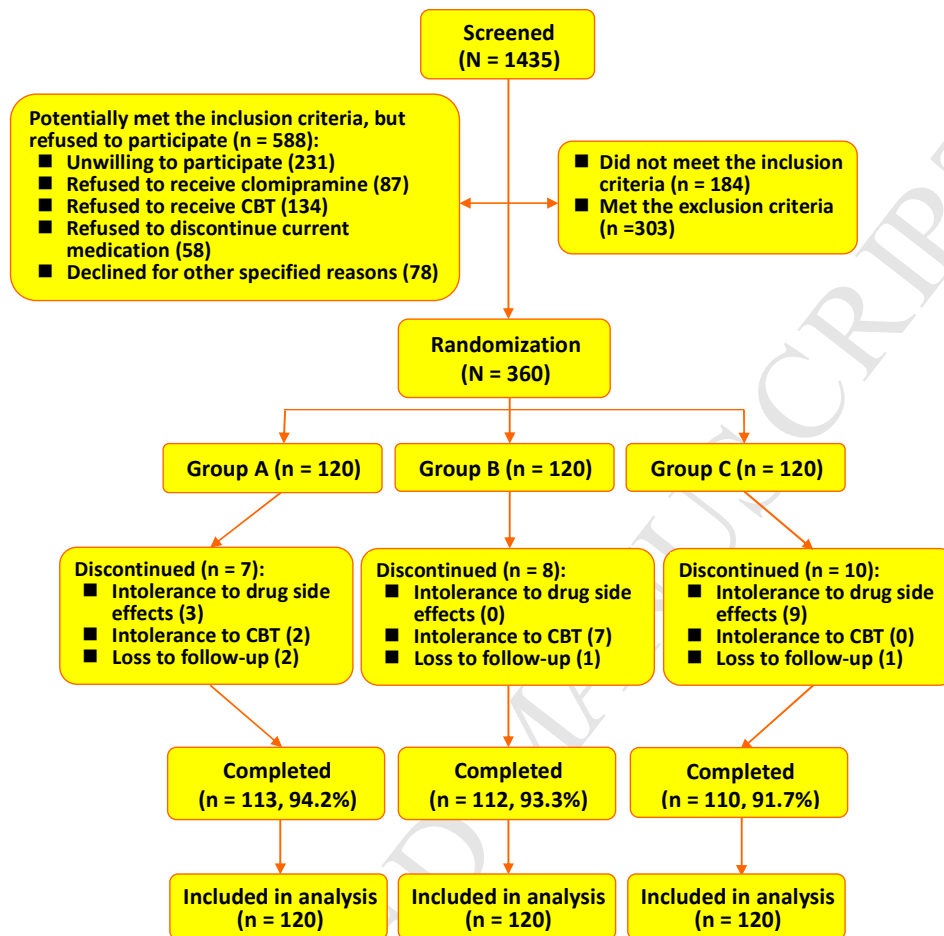


Fig. 2

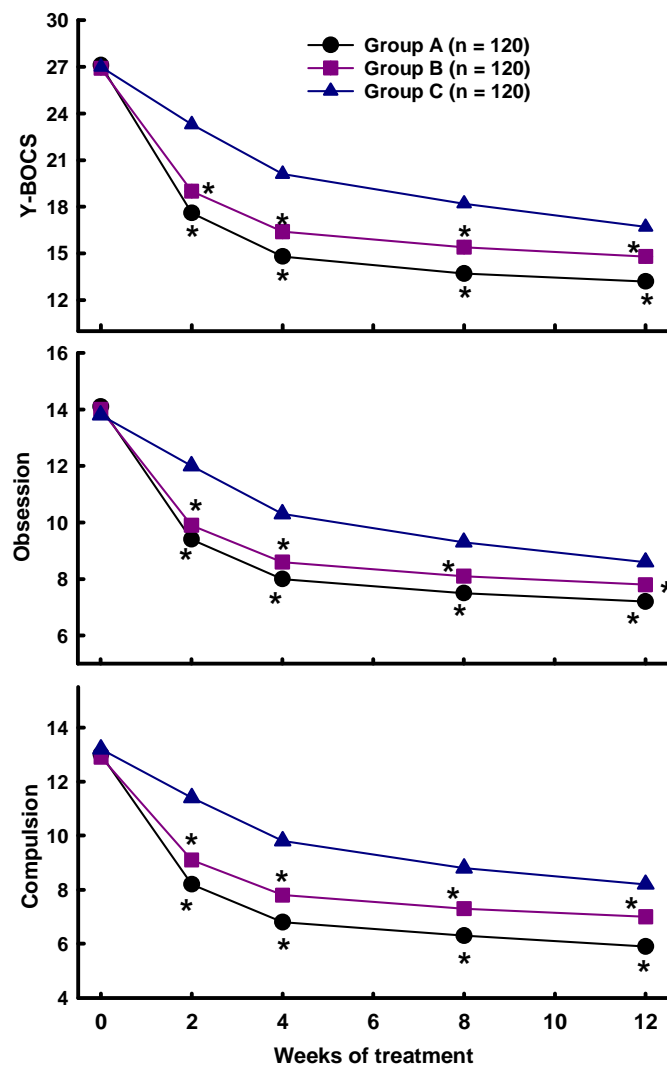
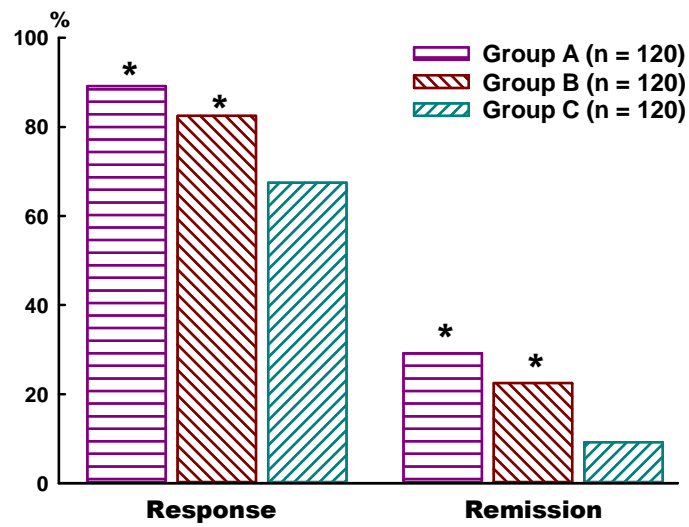


Fig. 3

**Fig. 4**

**Contributors**

BY and ZZJ were involved in conception and design of the study, data analysis and preparation of the manuscript. RMZ, GZY, LiYL, FZX, JC, LYL, YYL, YZ, and LXZ recruited subjects, conducted clinical assessment, and collected data. HKW performed data analysis. GMM provided critical comments on the paper.